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The Effect of Urography on Renal Function in Patients with Multiple Myeloma

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ABSTRACT

Reports in the medical literature of seven patients with multiple myeloma who died of acute renal failure following intravenous urography prompted a study of 39 patients with multiple myeloma who were subjected to intravenous urography at the Cleveland Clinic from 1940 to 1959. Four developed acute renal failure and two died within three weeks. All four revealed evidence of renal damage, or insufficiency, or both prior to urography. Thirty-five patients, 15 of whom had renal damage, had no untoward reaction to intravenous urography. These observations suggest that urography is associated with a small but definite risk in patients who have multiple myeloma and renal involvement.

SOMMAIRE

La presse médicale rapporte que sept malades atteints de myélomes multiples moururent après avoir subi une urographie intraveineuse; ces rapports furent à l'origine d'une étude portant sur 39 malades souffrant de myélomes multiples et soumis à une urographie intraveineuse entre 1940 et 1960. Quatre d'entre eux présentèrent de l'insuffisance rénale aiguë et deux moururent en moins de trois semaines. Avant l'urographie, les quatre malades présentaient des signes d'affection rénale ou d'insuffisance, ou même des deux. Trente-cinq malades, dont 15 présentaient une néphropathie, ne manifestèrent aucune réaction inquiétante après l'urographie intraveineuse. Ces rapports indiquent que l'urographie présente un danger réel, quoique minime, chez les malades atteints de myélomes multiples associés à une néphropathie.

IN 1954, Bartels *et al.*[1] were the first to report a case of acute oliguria and death which occurred after intravenous urography in a patient subsequently shown to have multiple myeloma (plasmacytic myeloma). Since that time, six similar cases have been reported.[2-5] Pertinent clinical data on these seven patients are summarized in Table I. In 1961, Leucutia[6] reviewed the subject and concluded that intravenous urography performed on patients with multiple myeloma carried a definite risk of producing renal failure. The probable mechanism, according to experimental and pathologic evidence, is one of intratubular precipitation of protein and severe tubular obstruction. It is possible that dehydration preceding urography, and abdominal compression during the procedure, are contributing factors.

Of the reported cases of renal failure, each patient who was tested had significant proteinuria, and each had Bence Jones proteinuria except the patient reported by Killmann, Gjorup and Thaysen.[3] On necropsy examination this was the only patient who did not have extensive cast formation in the renal tubules. The type of contrast medium administered seemed to be unrelated to the development of oliguria. Renal shutdown and oliguria usually occurred promptly after intravenous urography. Progressive uremia caused death in from nine days to three months, despite repeated hemodialyses in several cases. In the second patient reported by Myhre, Brodwall and Knutsen,[2] gradual recovery occurred with conservative management; over a period of seven months the blood urea content gradually decreased from 275 mg. per 100 ml. on the thirteenth day after intravenous urography to 106 mg. per 100 ml. at the time of death.

To assess the risk of producing this type of renal failure, case records were analyzed of all patients with proved multiple myeloma on whom intravenous urography had been performed at the Cleveland Clinic Hospital during the years 1940 to 1959 inclusive. A definite diagnosis of multiple myeloma, confirmed by bone marrow examination, was made in 227 patients during this period, of whom 39 underwent intravenous urography. Three of these patients had two intravenous urograms; two had a retrograde pyelogram following the intravenous urogram; and one had two intravenous urograms followed by a retrograde pyelogram (Case 1). There was clinical or laboratory evidence of deterioration in renal function soon after intravenous or retrograde urography in four of the 39 patients. The clinical data are summarized in Table I.

REPORT OF CASES

CASE 1.—A 42-year-old man was first examined at the Cleveland Clinic in August 1942, because of symptoms of multiple myeloma which began in June 1942.

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TABLE I.—CLINICAL DATA IN CASES OF RENAL FAILURE AFTER UROGRAPHY IN PATIENTS WITH MULTIPLE MYELOMA

Cases	*Age (yr.)*	*Sex*	*Initial blood urea, mg./100 ml.*	*Urine, specific gravity*	*Proteinuria*	*Bence Jones protein*	*Urographic contrast medium*	*Abdominal compression*	*Outcome*	*Renal lesion*
Bartels *et al.*,[1] 1954....	69	M	81	?	10 g./l.	?	20 ml. of iodopyracet 50% (Diodone)	Yes	Progressive uremia; death on 40th day	Many casts in tubules
Myhre, Brodwall and Knutsen,[2] 1956.....	70	M	30	1.029	18.5 g./l.	Positive	20 ml. of 35% Nycotrast	?	Progressive uremia; death on 11th day	No post-mortem study
Myhre, Brodwall and Knutsen,[2] 1956.....	42	M	36	1.032	12 g./l.	Positive	25 ml. of 35% Nycotrast	?	Oliguria two weeks; gradual recovery; death in seven months	Casts in tubules and interstitial infiltrate
Killmann, Gjorup and Thaysen[3] 1957.....	36	M	75-88 (Urea clearance) (BUN)	1.027	10-15 g./l.	?	35% iodopyracet (Diodone)	?	Oliguria; death on 9th day	Few casts
Perillie and Conn,[4] 1958	31	M	11	1.026	?	Positive	Sodium acetrizoate (Urokon)	?	Progressive uremia; death in three months	Tubules plugged with casts
Olmer *et al.*,[5] 1962.....	68	M	55	?	7 g./l.	Positive	?	Yes	Progressive uremia; death in 1½ months	Tubular casts and crystals
Olmer *et al.*,[5] 1962.....	42	F	50	?	19 g./l.	Positive	?	Yes	Progressive uremia; death in two months	No post-mortem study
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1	42	M	156	1.015	3+	Positive	Iodopyracet (Diodrast)	No	Progressive uremia after retrograde pyelography; death in 23 days	No post-mortem study
2	60	M	?	?	2+	Negative	Iodopyracet (Diodrast)	No	Progressive uremia; death from pneumonia in two weeks	Many tubular casts with desquamated epithelium
3	44	M	69	1.010	3+	?	Iodopyracet (Diodrast)	No	Rise of blood urea to 100 mg. per 100 ml. with gradual return to normal; death in three months	No post-mortem study
4	63	M	126	1.006	3+	Negative	Sodium acetrizoate (Urokon)	Yes	Oliguria and uremia after retrograde pyelography; gradual recovery. Sudden death two months later	Tubular obstruction by casts

The diagnosis was proved by bone marrow aspiration study. At that time the blood hemoglobin value was 68%. The red blood cell count was 3,500,000 per c.mm., and the white blood cell count, 9600 per c.mm. The differential white blood cell count was normal. Urinary symptoms included frequency every two to three hours, and nocturia, two or three times each night. Urinalysis revealed a specific gravity of 1.015, 3+ proteinuria, and many white blood cells. The test for Bence Jones proteinuria was positive. The blood urea value was 156 mg. per 100 ml. The serum albumin was 4.0 g. per 100 ml., and the serum globulin, 5.0 g. per 100 ml. An intravenous urogram, using iodopyracet (Diodrast), was performed on the second day in the hospital and was reported as demonstrating poor renal function bilaterally with inadequate visualization of the renal pelves. Treatment with intravenous administration of fluids was followed by a decrease in the blood urea concentration to 51 mg. per 100 ml. The urine culture was reported as positive for *Micrococcus pyogenes albus*. The intravenous urogram was repeated on the fourteenth day in the hospital, but could not be interpreted because of residual barium in the intestinal tract. The blood urea value on the sixteenth day was 39 mg. per 100 ml. On August 21 (the seventeenth day), bilateral retrograde pyelograms were made and the findings were normal. A high fever developed shortly after this procedure, with an increase in blood urea concentration and marked pyuria. Nine days after the retrograde pyelograms were made the blood urea concentration had risen to 342 mg. per 100 ml., at which time the patient was transferred to his local hospital where, 10 days later, he died. No postmortem examination was performed.

CASE 2.—A 60-year-old man was admitted to the hospital in September 1945, because of symptoms of multiple myeloma, first noted in August 1945. The diagnosis was confirmed by sternal bone marrow aspiration examination. Urinalysis revealed 2+ proteinuria, four white blood cells per high-power field, 8 to 10 red blood cells per high-power field, and numerous casts. The test for Bence Jones proteinuria was negative. The blood hemoglobin value was 8.8 g. per 100 ml.; and the packed cell volume was 26%. The white blood cell count was 9350 per c.mm., with a normal differential count. The serum calcium value was 14.5 mg. per 100 ml. and the serum phosphorus was 4.2 mg. per 100 ml. The serum albumin value was 1.9 g., and that of the serum globulin 3.5 g. per 100 ml. An intravenous urogram (with Diodrast) was performed on September 12 and revealed no visualization of the contrast medium. Two days after the procedure the blood urea value was 84 mg. per 100 ml., with a urea clearance of 29% in the first hour and 19% in the second hour. The patient's condition deteriorated rapidly, and by September 22 it was considered on clinical grounds that he was in renal failure. Unfortunately, further laboratory data were not available. The patient died on September 28, 1945, 14 days after the intravenous urogram had been made. The autopsy study confirmed the diagnosis of multiple myeloma and revealed homogeneous, pale-pink-staining casts in many of the renal tubules, with granular, swollen and desquamated tubular epithelium. In addition there was a bilateral bronchopneumonia.

CASE 3.—A 44-year-old man was admitted to the Cleveland Clinic Hospital in April 1949, because of symptoms of multiple myeloma since September 1948. The diagnosis was established by sternal bone marrow

examination, which showed 80% plasma cells. The blood hemoglobin value was 6.0 g. per 100 ml., and the hematocrit reading was 21%. The white blood cell count was 6300 per c.mm. The serum calcium value was 13.6 mg. per 100 ml. The only urinary symptom was urination of once each night. On April 5, 1949, the blood urea was 69 mg. per 100 ml. Urinalysis revealed a specific gravity of 1.010 with 3+ proteinuria, and a rare red blood cell per high-power field. The serum albumin value was 2.4 g. per 100 ml., and the serum globulin, 9.1 g. per 100 ml. An iodopyracet (Diodrast) intravenous urogram was performed the same day and revealed prompt bilateral excretion of the contrast medium but poor visualization of the renal pelves. An Addis count (without fluid restriction) was done two days later; there was a marked increase in white blood cells, red blood cells, and granular casts in the urinary sediment. The specific gravity was 1.014, and 2.7 g. of protein was excreted in the urine per 24 hours. The urine culture was sterile. Intravenous urography was repeated on April 18 and again showed poor renal function bilaterally. One week later the blood urea value was 100 mg. per 100 ml. The patient was not given specific treatment and the azotemia improved. On June 30, 1949, the blood urea value was 45 mg. per 100 ml. The patient died at home on July 14, 1949; autopsy was not performed.

CASE 4.—A 63-year-old man was admitted to the Cleveland Clinic Hospital in February 1954, because of bone pain since December 1953. The diagnosis of multiple myeloma was confirmed in February 1954, by examination of the bone marrow aspirate. The initial hemoglobin value was 13.6 g. per 100 ml. and the white blood cell count was 4400 per c.mm. He had urinary frequency and nocturia, three or four times each night. On February 8, 1954, the blood urea value was 126 mg. per 100 ml. The urinalysis revealed 3+ proteinuria, five white blood cells per high-power field, and a specific gravity of 1.006. The serum albumin value was 1.6 g., and the serum globulin 5.1 g. per 100 ml. An intravenous urogram with sodium acetrizoate (Urokon) was performed on February 8 with the use of abdominal compression. This study revealed poor bilateral renal excretion. Two days later the blood urea value was 123 mg. per 100 ml., with a urea clearance of 26% in one hour and 17% in the second hour. There was no change in his general condition and he was discharged from the hospital. Approximately one week later he was admitted to his local hospital, at which time bilateral retrograde pyelography was performed. Shortly thereafter oliguria developed, with fever, nausea, and vomiting. Three days later, on March 6, 1954, he was readmitted to the Cleveland Clinic Hospital. The blood urea value was 200 mg. per 100 ml. and the urinary output ranged between 500 and 1400 ml. per day throughout the next week. An Addis count (without fluid restriction) on March 8 showed 55,000,000 white blood cells, 4,500,000 red blood cells, and 25,000 casts. The corrected specific gravity was 1.009. The protein excretion was 1.1 g. in 24 hours. The urine culture revealed *Pseudomonas aeruginosa*. On March 11 the blood urea value had risen to 246 mg. per 100 ml. The test for Bence Jones proteinuria gave negative results. Therapy with intravenous injections of fluids and a low protein diet resulted in a gradual return of the blood urea to normal values, and a normal urinary output. On March 30 the blood urea value was 39 mg. per 100 ml. Analysis of the urine revealed less than 1 g. of protein excreted per 24 hours. On April 28 the patient suddenly died, possibly from septicemia. The necropsy examination confirmed the diagnosis of multiple myeloma. Microscopic examination of the kidneys revealed colloid casts obstructing many tubules. There was a foreign-body reaction around the tubules and an increased amount of periglomerular connective tissue. Amyloidosis was noted in the bone marrow.

COMMENT

The four patients described in this report had from 2+ to 3+ proteinuria before urographic examination. Three patients were tested for Bence Jones proteinuria, and a positive reaction was found in one. The blood urea value was elevated in three patients, and was probably elevated in the fourth, before intravenous urography was performed. Serum calcium content was high in both cases in which it was determined. The serum globulin value was elevated in all four patients. Two of the patients showed no adverse effects from one or more intravenous urograms, but severe renal failure developed after retrograde pyelography. In both of these patients urinary tract infection ensued, and was probably a major contributing cause of death. These two patients apparently are the first to be reported in whom acute renal failure was precipitated by retrograde pyelography in the presence of multiple myeloma.

Cases 3 and 4 suggest that the renal failure was at least temporarily reversible, even when it appeared to be of a severe degree. This has also been observed in many cases of multiple myeloma with spontaneous renal shutdown.[7]

Of the 35 patients who tolerated intravenous urography without obvious change in renal function, the resulting films were unsatisfactory in 11. This was usually due to poor excretion of the contrast medium and inadequate visualization of the pelvocalyceal systems. There was no discernible difference between the four patients adversely affected by intravenous or retrograde urography and the 35 in whom no complications developed. In the latter group, preceding intravenous urography the blood urea values were less than 40 mg. per 100 ml. in 17 patients, elevated (45 to 165 mg. per 100 ml.) in eight, and not determined in 10. Of the 20 patients tested for Bence Jones proteinuria, 11 had positive results. The serum globulin values exceeded 3 g. per 100 ml. in 11 of 21 of this group. The serum calcium values were greater than 11 mg. per 100 ml. in three of nine of these patients. To illustrate the unpredictability of the development of renal failure, seven patients with Bence Jones proteinuria and evidence of renal involvement in the form of albuminuria and/or azotemia tolerated intravenous urography without incident. It was not possible to determine which patients before urography had undergone purgation or dehydration, but these procedures have been rarely employed since 1945.

DISCUSSION

The impaired status of renal function in patients with multiple myeloma has been receiving increased attention. The blood urea value has been found to be elevated in from 25 to 57% of patients in different series.[8] Sanchez and Domz[9] stated that ". . . uremia is second only to pneumonia as a cause of death in those with multiple myeloma." Additional studies have shown impairment of renal function in approximately 50% of all patients with myelomatosis.[10, 11] Measurements of glomerular filtration rate, renal plasma flow, filtration fraction, and tubular excretory function have suggested the presence of a purely obstructive lesion in two series (19 patients); a more complex pattern is suggested in another series of 15 patients, namely that the glomerular function is more impaired than the tubular function.[11, 13] Albuminuria is found at some time during the course of the disease in 90% of patients with multiple myeloma. Albuminuria would not be expected with simple uncomplicated tubular obstruction. Bence Jones proteinuria is also found in from 50 to 60% of patients with myeloma during the course of their illness.[9] In one series of 97 patients, urinalysis disclosed abnormal numbers of white blood cells, red blood cells, and casts in 65%, 45% and 19%, respectively.[10] Of 65 patients tested for phenolsulfonphthalein excretion, half of them excreted less than 60% in two hours, and one-third excreted less than 40% in two hours.[10]

In addition to acute and chronic renal insufficiency, abnormalities of renal function have been described in patients with myeloma, including the nephrotic syndrome, water-losing nephritis, "adult Fanconi syndrome", and renal tubular acidosis.[6, 8, 9] Many different microscopic renal lesions have been noted in patients with multiple myeloma, but the most frequent and striking is that of "myeloma kidney". Amorphous eosinophilic material, sometimes laminated, is found in all portions of the tubule, often with tubular dilatation. A foreign-body reaction to this material is often present, with multinucleated giant cells. The tubular epithelium is flattened and desquamated. Similar material in the form of hyaline droplets or crystals may be present in the tubular cells, and may be the cause of impairment of function in patients without tubular obstruction.[6, 10] The degree of cast formation and tubular obstruction is not definitely correlative with the degree of renal dysfunction.

Studies of renal function in patients with hypercalcemia indicate a reduction in glomerular filtration rate and an impairment of renal concentrating ability.[12] A reduction of glomerular filtrate would seem to favour intratubular cast formation. The combination of hypercalcemia and abnormal protein in patients with multiple myeloma may thus be particularly unfavourable.

Although little detailed information is available concerning the effect on the normal kidney of intravenous contrast media in the concentrations used in urography, the risk of producing acute oliguria by intravenous urography in patients without multiple myeloma is apparently negligible. E. P. Pendergrass *et al.*[14] and H. P. Pendergrass *et al.*[15] reported an estimated incidence of less than one in one million. Berlyne and Berlyne[16] reported a single case of acute renal failure after intravenous urography, with recovery. In 1955 Alwall, Erlanson and Tornberg[17] reported 11 cases of renal failure, with seven deaths, following either intravenous urography or retrograde pyelography or both procedures. Of particular interest was their Case 9, a 43-year-old man whose only symptoms arose from fractured ribs. Upon routine examination, proteinuria was found, and for this reason intravenous urography was performed, with subsequent precipitation of acute oliguria. On roentgen examination the kidneys were reported to be "very large". He died two weeks later of "eclampsia [*sic*] and pulmonary edema." There was no proof that this patient had multiple myeloma but these features are most suggestive.[17]

Observations on the reactions of small blood vessels at the corneal-scleral junction after intravenous injection of urographic contrast medium suggest that there is a significant slowing of the microcirculation by these substances, because of vasoconstriction and clumping of the red blood cells.[18] If such a reaction occurs in the kidney, it would probably contribute to any renal damage produced.

It is difficult to assess the risk of intravenous urography in patients with multiple myeloma unless we know the incidence of "spontaneous" acute oliguria and uremia in such patients. It is recognized that such an event occurs, and at least six such cases have been reported.[19] The renal lesions in these cases are identical with those seen in patients after intravenous urography. The actual incidence of "spontaneous" acute oliguria and uremia in patients with myeloma has not been reported in any large series. Acute oliguria may develop in the presence of chronic renal insufficiency associated with multiple myeloma, and appears to be precipitated by fever and vomiting, with resultant dehydration. It also may be transient and resolve spontaneously, thus passing unrecognized during the course of the disease. Three patients with multiple myeloma and chronic renal insufficiency with superimposed acute oliguria were treated by Kolff[7] at the Cleveland Clinic. These patients recovered from the acute oliguria but died, within from one to three years later, of progression of their primary disease.

The precipitation of azotemia or aggravation of pre-existing azotemia or uremia after intravenous or retrograde urography in the reported cases and in the present series appears to indicate a causal rather than a coincidental relationship. The precipitation of protein in the tubular lumen with tubular dilatation is the most common lesion found at autopsy, and appears to be the most likely major cause of renal insufficiency. The factors responsible

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for such aggravation are not clear, but dehydration both from water restriction and from purgation probably is of importance. Abdominal compression with decreased renal tubular flow would also favour such precipitation.

CONCLUSION

A review of the records of 39 patients with multiple myeloma, who underwent intravenous and, in some instances, retrograde urography, revealed that in four patients renal failure quickly developed. The renal lesions in multiple myeloma are discussed and factors possibly responsible for the onset of acute oliguria and azotemia are analyzed. It is concluded that there is a small but definite risk of producing transient to fatal renal failure in patients with multiple myeloma, either by retrograde or by intravenous urography.

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